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Principal component analysis of the EEG spectrum can provide yes-or-no criteria for demarcation of boundaries between NREM sleep stages

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ABSTRACT

Human sleep begins in stage 1 and progresses into stages 2 and 3 of Non-Rapid-Eye-Movement (NREM) sleep. These stages were defined using several arbitrarily-defined thresholds for subdivision of albeit continuous process of sleep deepening. Since recent studies indicate that stage 3 (slow wave sleep) has unique vital functions, more accurate measurement of this stage duration and continuity might be required for both research and practical purposes. However, the true neurophysiological boundary between stages 2 and 3 remains unknown. In a search for non-arbitrary threshold criteria for distinguishing the boundaries between NREM sleep stages, scores on the principal components of the electroencephalographic (EEG) spectrum were analyzed in relation to stage onsets. Eighteen young men made 12–20-minute attempts to nap during 24-hour wakefulness. Single-minute intervals of the nap EEG records were assigned relative to the minute of onsets of polysomnographically determined stages 1, 2, and 3. The analysis of within-nap time courses of principal components scores revealed that, unlike any conventional spectral EEG index, score on the 4th principal component exhibited a rather rapid rise on the boundary between stages 2 and 3. This was mostly a change from negative to positive score. Therefore, it might serve as yes-or-no criterion of stage 3 onset. Additionally, similarly rapid changes in sign of scores were exhibited by the 1st and 2nd principal components on the boundary of stages 2 and 1 and on the boundary between stage 1 and wakefulness, respectively.

1. Introduction

Scientific study of human sleep has been initiated by the discovery that sleep progresses through a series of stages in which different brain wave patterns are displayed (e.g., [6]). Indeed, visual analysis of most of polysomnographic sleep records reveals that human sleep begins in stage 1 (N1) and progresses into stages 2 (N2) and 3 (N3) of Non-Rapid-Eye-Movement (NREM) sleep. The conventional methodology of such subdivision of the sleep records into intervals each of

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which is allocated to one of a few all-or-nothing variables called "sleep stages" has been first introduced in 1968 in the publication of the standard sleep scoring rules [20]. Since some of these rules, especially with respect to stage boundaries, are difficult to follow, this standard system of sleep description faces practical problems of definition and demarcation of sleep stages [24,23]. Nevertheless, the criteria for distinction between stages 1 and 3 of NREM sleep had remained almost unchanged after rare attempts to revise these criteria [3,24].

One of the major shortcomings of the standard scoring rules is their relying on arbitrarily-defined thresholds for separation of NREM sleep stages. For instance, the most powerful component of the electroencephalographic (EEG) signal, delta activity (slow waves with frequencies 0.5–4.5 Hz), exhibits a gradual increase in the course of sleep deepening that starts with a short transitional interval known as stage 1 (N1), continues through the following much longer interval of stage 2(N2) that is viewed as the first unequivocal stage of sleep and reaches its peak during stage 3 (N3) that is usually named slow wave sleep (SWS) due to predominance of relatively high-voltage (more than 75 μV) low-frequency waves (0.5–2.0 Hz). The arbitrarily-defined threshold criteria that were recommended for defying stage 3 (N3 or SWS) include three (amount, frequency and amplitude) thresholds, i.e., more than 20% of <2 Hz activity with amplitude >75 μV during a given epoch of sleep [20,3]. Therefore, subjective assessment of the EEG epochs is necessary and this can lead to unreliable results and poor agreement between scorers [4]. Particularly, Norman et al. [10] reported that stages N1 and N3 are most prone to disagreement, and that, overall, 88.4% of the scoring disagreements are associated with scoring adjacent stages (wake/N1, N1/N2, and N2/SWS).

Until recently, SWS and slow-wave activity have been simply viewed as useful objective markers of sleep deepness and intensity. However, most recent studies showed that they might be of particular importance for analysis of the sleep process due to their unique vital functions. For example, these studies point to their essential role in learning and memory (e.g., [7,19,5,26,25]). Since the presence and integrity of SWS was found to be linked to the ability to form and retain memories, the diminished levels of conventionally scored stage 3 sleep can explain some cognitive impairment in primary insomnia and older age (e.g., [1,9]). Therefore, one of the questions that need to be answered in the light of such recent findings might be: where is the true neurophysiological boundary between stages 2 and 3 (N2/N3)?

Earlier we showed that principal component structuring of the EEG spectrum provides a theoretically sound method of relating the quantitative descriptions of spectral power densities to quantitative changes (i.e., from negative to positive) in scores on the largest principal components of the EEG spectrum [11–15,17,16,18]. It was hypothesized that the rise of the 1st score reflects the switch-like change in the sleep-promoting processes that usually delays relative to the change in the wake-promoting processes represented by the decline of the 2nd score [11,16]. Consequently, stage 1 sleep might be viewed as "no man's land" between the opponent driving forces for wake and sleep [14,15]. It was also shown that, like it occurs during diurnal sleep-wake transitions, the 1st and 2nd components of the EEG spectrum might also represent alternations between competing drives for sleep and wakefulness throughout the whole episode of all-night sleep, whereas time courses of the next pair of component scores (3rd and 4th) might reflect the within-sleep alternations between sub-sates of light and deep sleep, respectively [11,12]. At least, the time course of the 4th score during each ultradian sleep cycle pointed to its link to deep sleep, i.e., its rapid raise always delayed relative to changes in the 1st and 2nd scores in the beginning of the first sleep cycle, but its maximum was reached already in the middle of the cycle, and its fall during the second half of the cycle occurred earlier compared to changes in other scores [11,12].

However, it remains unclear whether the rapid rise of the 4th principal component score precedes or coincides with or follows the transition from stage 2 to stage 3 sleep. Empirical support of the suggestion of stable phase relationship of such a rise with the conventionally scored onset of stage 3 can open a perspective of identification of non-arbitrary (i.e., neuro-physiologically meaningful) boundaries between stages 2 and 3. Therefore, the present analysis was aimed on testing the hypothesis that the rapid rise of the 4th principal component score coincides with the transition to stage 3, whereas the rapid changes in the 1st and 2nd scores are not associated with this transition but, instead, linked to the boundaries of two earlier NREM sleep stages.

2. Methods

The experimental study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Its protocol was approved by the Ethics Committee of the Siberian Branch of the Russian Academy of Medical Sciences (#2/07.06.2009). Informed written consent was obtained from each study participant. The analyzed data set contains spectra of the EEG signals recorded from 18 male cadets of the Novosibirsk military high school. Their ages ranged from 18 to 22 years. Their regular sleep prior to the experiments occurred within 7-hour interval between the rising and bedtimes scheduled on 06:30 and 23:30, respectively. The experiments were carried out in the laboratory complex on 9 weekends, between Saturday morning and Monday morning, with 2 participants studied during each weekend. They both were kept continuously awake until 23:00, and then one of them was allowed to sleep in the sleep laboratory until 06:00 h. The other was kept awake for the whole night. The next 24 h were organized in 12 wake–sleep cycles each consisting of 100-minute wakefulness followed by 20-minute nap with polysomnographic recordings. A participant was asked to sleep lying in bed in a sound-attenuated and completely darkened room of the sleep laboratory during a 20-minute span with closed eyes. Then he was taken out of the sleep laboratory to stay in other rooms together with experimenters for the whole time interval between consecutive napping attempts. To prevent unintended sleep, he was constantly engaged in research activities and social interactions.

Polysomnographic sleep recordings were performed using a standard monitoring montage that included 5 EEG channels, two electro-oculogram channels, and one chin electromyogram channel. Data were collected via an 8-channel Medicor polygraph (EEG8S, Micromed, Hungary). Since the central derivations were recommended for visual scoring of sleep stages

[20,3], the reported results are based on data from Cz-A1 derivation of the international 10–20 system of electrode placement (i.e., vertex of the head vs left mastoid). Conventional scoring of 20-min naps was performed by 2 independent judges. Thereafter, they together reexamined the epochs with discrepant scores in order to produce consensus scores.

The EEG signals were high band-pass, low band-pass, and notch filtered (0.5, 64, and 50 Hz, respectively), digitized at a sampling frequency of 128 Hz and stored on a hard disk. The artifacts were detected at 5-second intervals, and absolute power values were computed for the artifact-free 5-second intervals using the fast Fourier transform algorithm. The spectral data were reduced to single-hertz bin widths by calculating the mean absolute power values over adjacent frequencies and by further averaging within each consecutive one-minute interval.

The one-min spectra calculated for each 20-min nap were assigned relative to 0-minutes of polysomnographically determined onset of stage 1 (N1), stage 2 (N2), and stage 3 (N3). In total, 164 naps were used for the present analysis after exclusion of a few naps either containing REM sleep or showing that NREM sleep was interrupted by wakefulness. Spectra on the interval of the first 16 power values (the range from 1 to 16 Hz) were log-transformed and subjected to principal component analysis. Additionally, the log-transformed power values were averaged over frequency ranges roughly corresponding to delta, theta, alpha, and sigma activities (1–4, 5–8, 9–12, and 13–16 Hz, respectively). The SPSS statistical software package, version 21, was used for all statistical analyses (SPSS, Chicago, IL). Principal component analysis was run either on all sets of spectra or on the sets obtained from each of 18 participants (Fig. 1A and B). Each set was decomposed into four principal component scores. In order to calculate a score on each of the four components, the 16 original power values were optimally weighted in accord with their loadings on this component (Fig. 1A) and then summed. More details regarding the methodology of principal component analysis of the EEG spectrum have been reported earlier [11,12,17,18].

In order to analyze and illustrate (Table 1, Figs. 2–3) steepness of changes in the EEG indexes during transitions from one stage to another, one-min values were further averaged on 3-min intervals (i.e., from minute −4 to −2, from −1 to +1, from +2 to +4, etc.). Additionally, all positive and negative one-min scores on a component (i.e., 1st or 4th) were transformed into +1 and 0, respectively, for illustrating time courses of probability of association of a stage (i.e., 2 or 3) with positive score on a component (Fig. 4).

One-way repeated-measure analyses of variance (rANOVAs) with within-subjects factor "Three-min interval" were performed for examining whether an EEG index ehibites statistically significant changes both prior to and after onset of a stage. The Bonferroni multiple comparison test was used in the post hoc analysis, i.e., for examining significance of differences between a value of an index for 0-minute of stage onset and

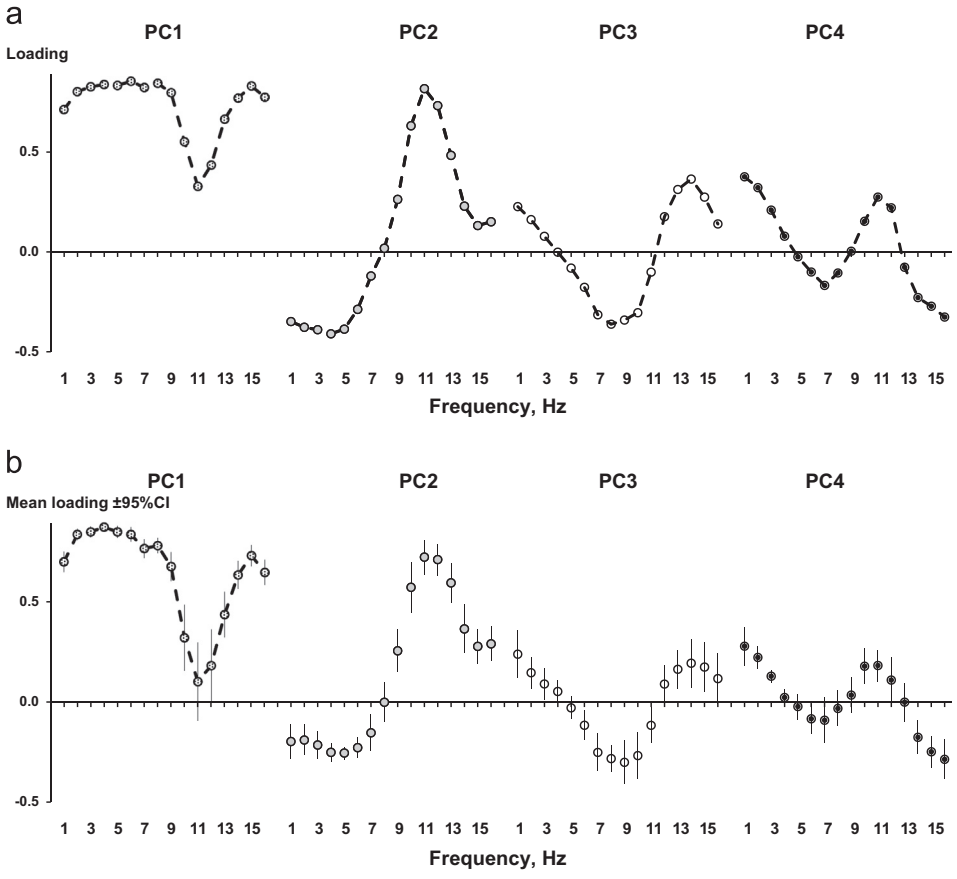

Fig. 1 – Loading spectra of the four largest principal components of the EEG spectrum. Loading spectra for the 1st–4th principal components (frequency range between 1 and 16 Hz) were calculated for the whole data set (A) and separately for each of 18 study participants (B). Individual loadings were then averaged drawn as Mean loading ± 95% Confedence Interval.

Table 1 – Change in the EEG indexes before and after onsets of NREM sleep stages 1, 2, and 3.

Sleep stage	N1 (sleep onset)		N2 (stage 2 sleep onset)		N3(stage 3 sleep onset)	
EEG index	−3 vs. 0	0 vs. +3	−3 vs. 0	0 vs. +3	−3 vs. 0	0 vs. +3
Delta power	−0.18***	−0.40***	−0.35***	−0.27***	−0.27***	−0.20***
Theta power	−0.14**	−0.34***	−0.32***	−0.25***	−0.05	−0.02
Alpha power	0.29***	0.13**	−0.00	−0.13**	−0.09**	0.02
Sigma power	0.07	−0.09*	−0.14***	−0.26***	−0.07	0.09
Score on PC1	−0.04	−0.45***	−0.50***	−0.52***	−0.25***	−0.05
Score on PC2	0.77***	0.73***	0.41***	0.00	0.05	−0.25
Score on PC3	−0.01	0.16	0.14	−0.07	−0.32	0.05
Score on PC4	0.21*	0.19	0.10	0.16	−0.62**	−0.64**

Note. PC1-PC4: 1st–4th principal components of the EEG spectrum. Values of an EEG index were calculated for three 3-min intervals of the nap EEG record before (−3), during (0) and after (+3) onset of sleep stages 1 (N1), 2 (N2), and 3 (N3) of NREM sleep (n=17, 18, and 12, respectively). Wakefulness state was (N1) or was not accounted (N2 and N3). Results of one-way repeated measure ANOVAs with within-subjects factor "Three-min interval" (−3, 0, and +3);
Level of significance for difference between two values (results of post-hoc pairwise comparisons with Bonferroni adjustment for the number of comparisons).
*** ($P<0.001$).
** ($P<0.01$).
* ($P<0.05$).

the preceding and following values (Table 1). Additionally, 2-way ANOVAs were run on time courses of the EEG indexes (Fig. 2) with fixed factor "Interval", i.e., either "Three-min interval" (Fig. 3B) or "One-min interval" (Fig. 4), and random factor "Participant" (Fig. 3A). Finally, two-way ANOVAs with two fixed factors were conducted on these time courses to test whether they are different for different experimental conditions, times of day, delays of stage onset, etc. The first fixed factors was "Three-min interval" and the second was, respectively, "Condition" (sleep deprived vs. slept), "Time of day" (12 clock times; Fig. 3A), "Stage onset delay" (minutes −12, −9, −6, −3, and 0), etc.

3. Results

Principal component analysis yielded the first four eigenvalues that were either remarkably higher than 1 (the 1st and 2nd) or close to 1 (the 3rd and 4th). These four principal components collectively explained for almost 84% of the total variance of the EEG spectrum (55%, 18%, 6%, and 5%, respectively). The shapes of principal component loadings are illustrated in Fig. 1 by plotting the loadings of the 16 powers on each component as a function of frequency band. The shapes of such loading spectra obtained for the whole dataset were very similar to those obtained for any study participant (Fig. 1A and B, respectively). Therefore, only scores calculated for the whole dataset were used in further analysis.

Fig. 2 demonstrates that time courses of spectral powers and principal component scores were often characterized by very steep changes either before or after or both before and after onset of a certain sleep stage. Table 1 reveals that such changes cannot be regarded as being stage-specific in the case of low frequency powers (i.e., delta and theta) that always dominated during well-established sleep. For instance, delta power exhibited steep rises both before and after onsets of all three stages. In contrast, steep changes in high frequency powers (i.e., alpha and sigma) were specifically linked to onset of a certain stage, i.e., they showed steep rises both before and after onset of only one of three stages. As one can predict from the conventional sleep scoring rules, the steep decline of alpha power occurred around sleep onset (i.e., it reflects the phenomenon of attenuation of alpha rhythm during transition from wakefulness to stage 1 sleep), whereas sigma power exhibited its steep rise around onset of stage 2 sleep (i.e., it is associated with typical short sequences of waves of 11–15 Hz called "sleep spindles").

Table 1 and Fig. 2B indicate that rapid changes in scores on the 1st, 2nd, and 4th principal components were linked to onset of only one of three stages (2, 1, and 3, respectively), and that the transition from one stage to another was associated with a change in the sign of score (from positive to negative for 2nd score and from negative to positive for 1st and 4th score). Fig. 3A illustrates that the records obtained for 12 different clock times were similar on the time courses of scores on the 1st, 2nd, and 4th principal components around onsets of stages 2, 1, and 3, respectively. As indicated by the results of two-way ANOVAs with the first factor "Three-min interval" and the second factor either "Condition" (sleep deprived vs. slept) or "Time of day" (12 clock times; Fig. 3A) or "Delay of stage onset" (minutes −12, −9, −6, −3, and 0), neither significant main effect of the second factor nor interaction between the two factors were significant. Fig. 3B illustrates remarkable similarity between participants on the time courses on scores on the 1st, 2nd, and 4th principal components. For instance, 4th score always become positive when sleep of a given study participant progressed into SWS.

Fig. 4 summarizes the results on the time courses of principal component scores. As it was suggested (see Introduction), the 2nd score became negative on the borderline between wakefulness and sleep, and it remained negative during well-established sleep. Rapid buildup of the 1st score was a feature of transition from stage 1 to stage 2, and stage 1 was almost always associated with negative rather than positive 1st score (Fig. 4A). The 4th score demonstrated its rapid raise during transition from stage 2

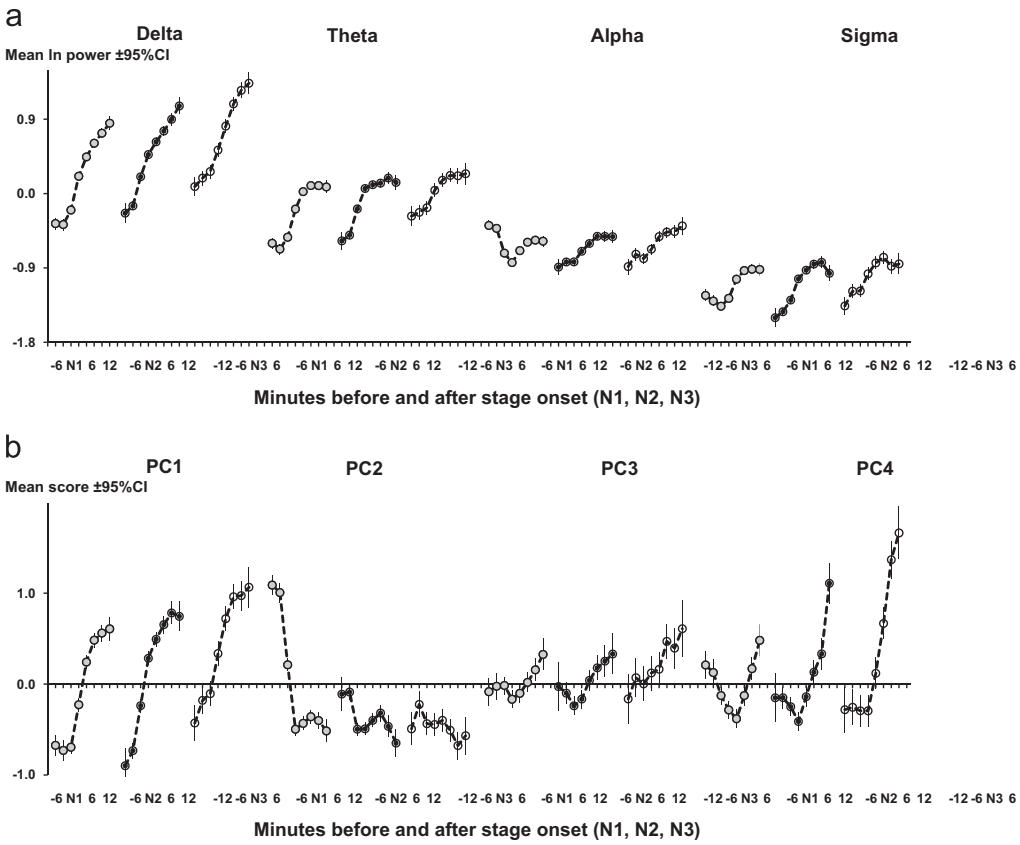

Fig. 2 – Time courses of spectal powers and scores on principal components.Single-Hz log-transformed spectral powers (ln power) were averaged over frequency ranges roughly corresponding to delta (1–4 Hz), theta (5–8 Hz), alpha (9–12 Hz), and sigma activity (13–16 Hz). The 1st–4th principal component scores and ln powers were aligned relative to the 0-minute of onset of NREM sleep stage 1 (N1), stage 2 (N2), and stage 3 (N3), and then averaged on 3-min intervals prior and after this minute (i.e., minutes from −4 to −2, from −1 to +1, from +2 to +4, etc.). Wakefulness was (N1) and was not accounted (N2 and N3). Results of two-way ANOVAs with fixed factor "Three-min interval" and random factor "Participant" ($n=14$ for N3 and $n=18$ for N1 and N2).

to stage 3, and, therefore, stage 3 was characterized by only positive scores (Fig. 4B).

4. Discussion

Because the conventional distinctions between sleep stages are mostly arbitrary, the true neurophysiological boundaries between these stages remain to be clarified. Besides, the computerized sleep EEG analysis indicates that NREM sleep stages seem to represent subdivision of a continuous process. Indeed, the present results confirmed the earlier reports (e.g., [8]) showing that such well-known marker of sleep deepness and intensity as delta power exhibits permanent increase in the course of sleep deepening (Fig. 2A and Table 1). On the contrary, the present analysis yielded the state-specific stepwise changes of the indexes obtained by means of principal component structuring of the EEG spectrum. It was found that, irrespective of experimental condition, nap timing, latency to sleep stage, and within-group individual differences, the boundaries of NREM sleep stages 1, 2, and 3 coincided with a rapid change in score on one of three principal components, i.e., 2nd, 1st, and 4th, respectively (Figs. 2B, 3 and 4; Table 1). In particular, the present results supported the hypothesis that the transition to stage 3 sleep (SWS) always coincides with a rapid switch from negative to positive score on the 4th principal component of the EEG spectrum (Figs. 3 and 4B). The results also demonstrated that, unlike the 4th score, the 1st and 2nd scores did not exhibit rapid changes both before and after onset of stage 3 (Table 1). Instead, such changes occurred on the boundaries of earlier NREM stages (Fig. 4) that is in agreement with our previously reported observations [14–16]. Thus, the results allow the conclusion that transitions to negative 2nd scores and to positive 1st and 4th scores might serve as yes-or-no criteria of onsets of "drowsy" sleep (stage 1), well-established sleep (stage 2), and SWS (deep sleep or stage 3), respectively (Fig. 4; Table 1).

Such results suggesting remarkable coincidence of conventionally scored onsets of three sleep stages with stepwise changes in principal component structure of the EEG spectrum might explain the unexpected success of the Rechtschaffen and Kales rules [20] that provided continuity in the scientific and clinical description of the sleep process for, at least, a half of century. The possibility to represent all various epochs of the continuous sleep process as a sequence of few all-or-nothing variables might be explained by such feature of sleep-wake

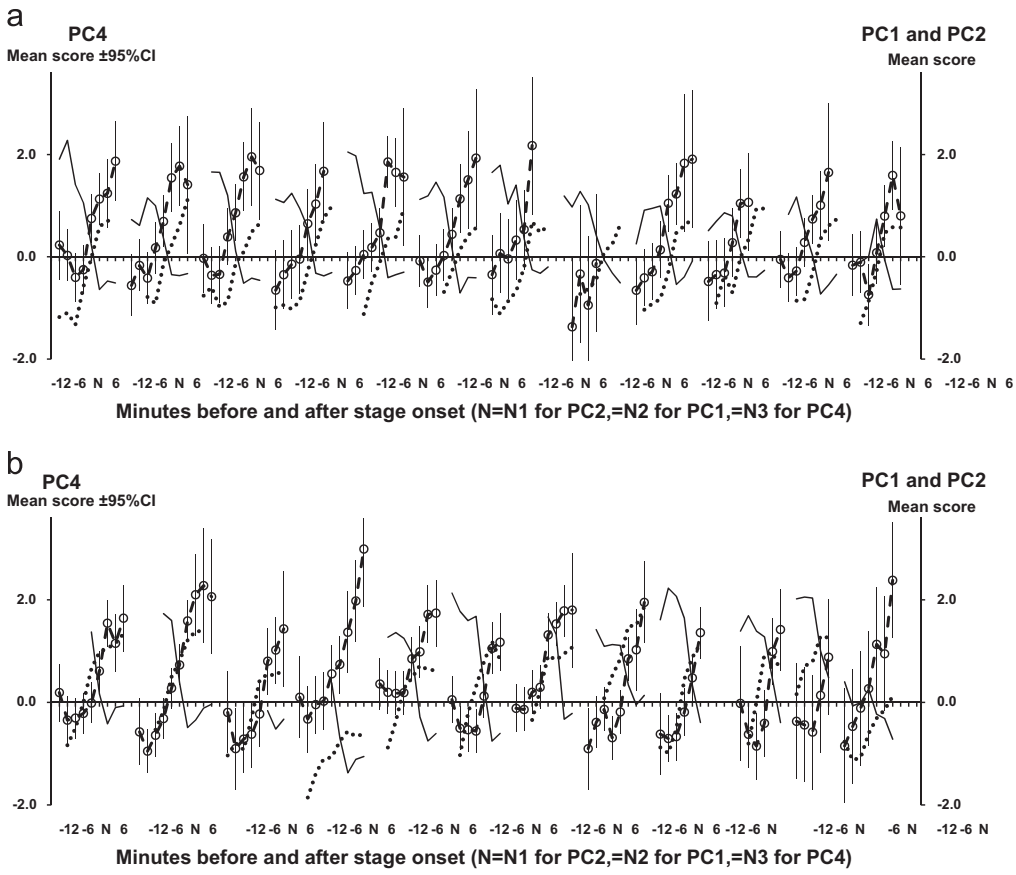

Fig. 3 – Time courses of score on the 1st, 2nd and 4th principal components.(A) Time courses of the 4th score (circles and dashed lines) for 12 clock times (from the 1st, 6:00–7:00, to the 12th, 4:00-5:00). Results of two-way ANOVAs with fixed factors "Three-min interval" and "Clock time". (B) Individual time courses of the 4th score (circles and dashed lines) for participants with, at least, one episode of SWS of more than three-minute duration. The first 9 participants were sleep deprived. Results of two-way ANOVAs with fixed factor "Three-min interval" and random factor "Participant" ($n=12$). For comparison, time courses of scores on the 1st and 2nd principal components are drawn relative to onsets of stages 2 and 1 sleep (dotted and solid lines, respectively). See also the legend to Fig. 2.

regulating mechanisms as reciprocal interactions between sleep- and wake-promoting processes that inhibit one another in the course of transitions between sleep/wake states and sub-states.

Particularly, complex neurobiological mechanisms of sleep and wakefulness can be, ultimately, delineated as oscillations between opposing processes, i.e., those promoting arousal and inhibiting sleep and those promoting sleep and inhibiting arousal (e.g., [2,22]) Recent research indicates that the ventrolateral preoptic nucleus of the hypothalamus contains both sleep-promoting neurons and wake-promoting neurons that control daily transitions between behavioral states of wakefulness and sleep as well as alternations between REM and NREM sleep [21]. Despite arbitrariness of threshold criteria used for distinction between sleep stages, the scoring rules uncovered the essential links of visually recognized changes in brain wave patterns with the most important switch-like transitions between wake/sleep states and sub-states. Particularly, the time course of score of the 2nd principal component characterized by the rapid decline around sleep onset (N1) might be interpreted as reflecting the major switch in regulation of wake/sleep pressure by the wake-promoting processes. The time course of the 1st principal component score with the rapid buildup during onset of well-established sleep (N2) might be regarded as representing the main switching point in regulation of sleep demand by the sleep-promoting processes. The time course of score of the 4th principal component that exhibits its rapid rise simultaneously with onset of SWS (N3) might reflect the switch-like alternations between sub-states of light and deep sleep within each ultradian sleep cycle [11–15].

It has to be emphasized that the present results have practical relevance to better understanding of sleep disorders associated with the reduced SWS and increased stage 1 sleep. Moreover, they also can be implicated in development of new technics of computerized sleep analysis. For instance, the results supporting the suggestion of the existence of the stable phase relationship between the rise of the 4th principal component score and the conventionally scored onset of N3 can facilitate the application of more accurate yes-or-no criteria into the computerized measurement of SWS duration and continuity in normal and disordered sleep.

Limitations of the present analysis include small sample size, absence of data on healthy participants of different genders and ages and on patients with different sleep disorders, lack of analysis of regional differences in the EEG indexes, a relatively

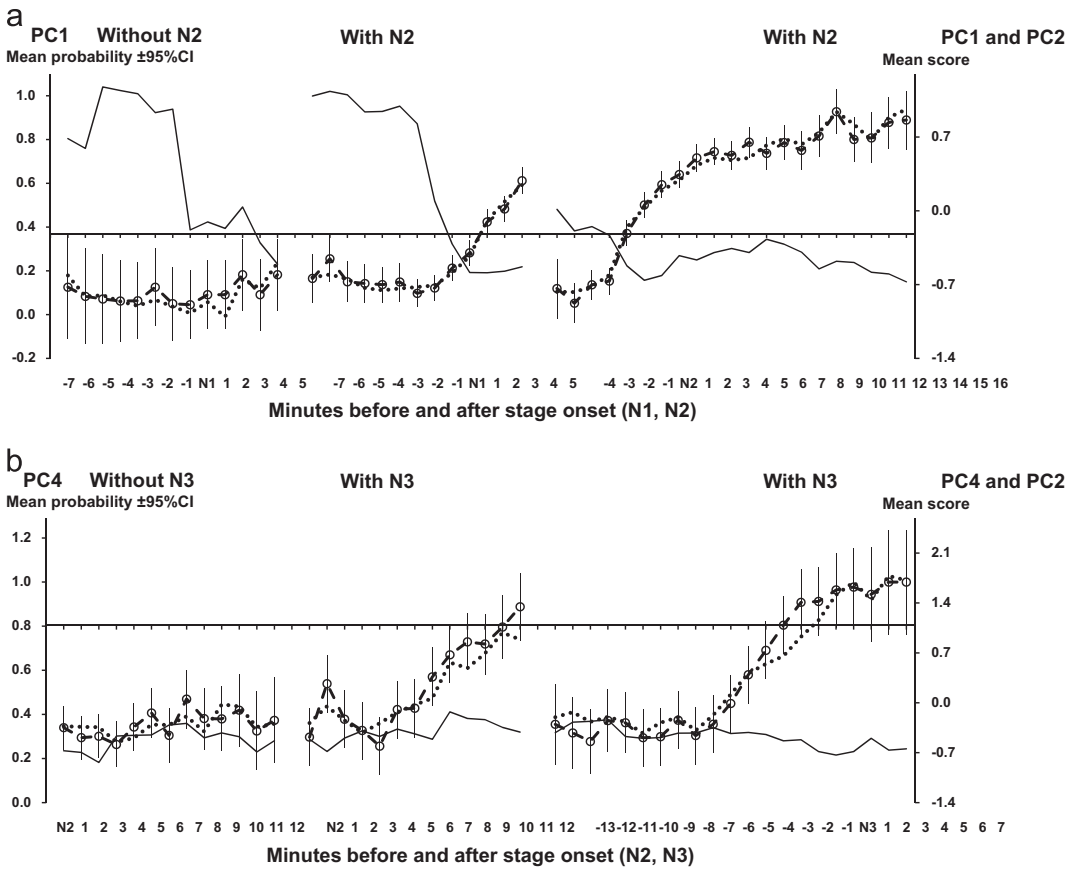

Fig. 4 – Time courses of probability of stages 2 and 3. (A) Time courses of scores on the 1st and 2nd principal components (dotted and solid lines, respectively) relative to onsets of stages 1 (N1) and 2 (N2), and time courses of probability of stage 2 (circles and dashed lines) determined by assigning the 1st score to 0 when negative and to +1 when positive. For N1 (left and middle plots), mean values were taken from results of three-way ANOVAs with random factor "Participant" ($n=11$ vs. 18) and fixed factors "One-min interval" and "N2" (With or Without N2 initiated within the first 6 min of sleep). For N2 (right plots), results of two-way ANOVAs with random factor "Participant" ($n=18$) and fixed factor "One-min interval". (B) Time courses of score on the 4th and 2nd principal components (dotted and solid lines) relative to onsets of stages 2 (N2) and 3 (N3), and time courses of probability of stage 3 (circles and dashed lines, respectively) determined by assigning the 4th score to 0 when negative and to +1 when positive. For N2 (left and middle plots), results of three-way ANOVAs with random factor "Participant" ($n=14$ vs. 18) and fixed factors "One-min interval" and "N3" (With or Without N3). For N3 (right plots), results of two-way ANOVAs with random factor "Participant" ($n=14$) and fixed factor "One-min interval". See also the legend to Fig. 2.

short duration of the EEG records, and relatively long intervals of data averaging. Future analyses lacking these limitations might provide a much deeper insight into temporal, topographic, and individual differences in changes in principal component scores across transitions between sleep stages. Moreover, further research is required for evaluating prospects of implication of principal component scoring in methods of measurement of duration and continuity of sleep stages, as well as for examining whether measures obtained with this method correlate with sleep-state-dependent functions (e.g., memory consolidation results) stronger than the conventional estimates of duration and continuity of sleep stages.

To conclude, the EEG indexes provided by applying principal component analysis to the EEG spectrum might be recommended for less arbitrary and physiologically meaningful subdivision of NREM sleep into stages 1, 2, and 3. In particular, positive score on the 4th principal component of the EEG spectrum might serve as both theoretically and practically useful yes-or-no criterion of SWS onset.

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REFERENCES

[1] Backhaus J, Junghanns K, Born J, Hohaus K, Faasch F, Hohagen F. Impaired declarative memory consolidation during sleep in patients with primary insomnia: influence of sleep architecture and nocturnal cortisol release. Biol Psychiatry 2006;60:1324–30.

[2] Boutrel B, Koob GF. What keeps us awake: the neuropharmacology of stimulants and wake-promoting medications. Sleep 2004;27:1181–94.
[3] Iber C, Ancoli-Israel S, Chesson AL, Quan SF. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Westchester, IL: American Association of Sleep Medicine; 2007.
[4] Kelley JT, Reed K, Reilly EL, Overall JE. Reliability of rapid clinical staging of all-night sleep EEG. Clin Electroencephalogr 1985;16:16–20.
[5] Landsness EC, Crupi D, Hulse BK, Peterson MJ, Huber R, Ansari H, Coen M, Cirelli C, Benca RM, Ghilardi MF, Tononi G. Sleep-dependent improvement in visuomotor learning: a causal role for slow waves. Sleep 2009;32:1273–84.
[6] Loomis AL, Harvey EN, Hobart GA. Cerebral states during sleep, as studied by human brain potentials. J Exp Psychol 1937;21:127–44.
[7] Marshall L, Molle M, Hallschmid M, Born J. Transcranial direct current stimulation during sleep improves declarative memory. J Neurosci 2004;24:9985–92.
[8] Merica H, Fortune RD. State transitions between wake and sleep, and within the ultradian cycle, with focus on the link to neuronal activity. Sleep Med Rev 2004;8:473–85.
[9] Nissen C1, Kloepfer C, Nofzinger EA, Feige B, Voderholzer U, Riemann D. Impaired sleep-related memory consolidation in primary insomnia–a pilot study. Sleep 2006;29:1068–73.
[10] Norman RG, Pal I, Stewart C, Walsleben JA, Rapoport DM. Interobserver agreement among sleep scorers from different centers in a large dataset. Sleep 2000;23:901–8.
[11] Putilov AA. Prospects of using electroencephalographic signatures of the chronoregulatory processes for meaningful, parsimonious and quantitative description of the sleep-wake sub-states. Biol Rhythm Res 2011;42:181–207.
[12] Putilov AA. Principal components of electroencephalographic spectrum as markers of opponent processes underlying ultradian sleep cycles. Chronobiol Int 2011;28:287–99.
[13] Putilov AA. Simulation of an ultradian sleep homeostasis through fitting time courses of its EEG indicators obtained during baseline recordings of night sleep. Biol Rhythm Res 2014;45:345–68.
[14] Putilov AA. When does this cortical region drop off? Principal component structuring of the EEG spectrum yields yes-or-no criteria of local sleep onset. Physiol Behav 2014;133:115–21.
[15] Putilov AA. Rapid changes in scores on principal components of the EEG spectrum do not occur in the course of "drowsy" sleep of varying length. Clin EEG Neurosci 2014;46 online first publication.
[16] Putilov AA, Donskaya OG. Rapid changes in scores on the two largest principal components of the electroencephalographic spectrum demarcate the boundaries of drowsy sleep. Sleep Biol Rhythms 2013;11:154–64.
[17] Putilov AA, Donskaya OG, Verevkin EG. Quantification of sleepiness through principal component analysis of the EEG spectrum. Chronobiol Int 2012;29:509–22.
[18] Putilov AA, Münch MY, Cajochen C. Principal component structuring of the non-REM sleep EEG spectrum in older adults yields age-related changes in the sleep and wake drives. Curr Aging Sci 2013;6:280–93.
[19] Rasch B, Buchel C, Gais S, Born J. Odor cues during slow-wave sleep prompt declarative memory consolidation. Science 2007;315:1426–9.
[20] Rechtschaffen A, Kales A, A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Los Angeles, CA: UCLA Brain Information Service/Brain Research Institute; 1968.
[21] Saper CB. The neurobiology of sleep. Continuum (Minneap Minn), 19; 19–31 (1 Sleep Disorders).
[22] Saper CB, Chou TC, Scammell TE. The sleep switch: hypothalamic control of sleep and wakefulness. Trends Neurosci 2001;24:726–31.
[23] Schulz H. Rethinking sleep analysis. J Clin Sleep Med 2008;4:99–103.
[24] Silber MH, Ancoli-Israel S, Bonnet MH, Chokroverty S, Grigg-Damberger MM, Hirshkowitz M, Kapen S, Keenan SA, Kryger MH, Penzel T, Pressman MR, Iber C. The visual scoring of sleep in adults. J Clin Sleep Med 2007;3:121–31.
[25] Van Der Werf YD, Altena E, Schoonheim MM, Sanz-Arigita E, Vis JC, De Rijke W, Van Someren EJW. Sleep benefits subsequent hippocampal functioning. Nat Neurosci 2009;12:122–3.
[26] Walker MP. The role of sleep in cognition and emotion. Ann NY Acad Sci 2009;1156:168–97.